REMARKS

Claims 1 to 26 are pending, with the nuclear hormone receptor species RAR and the coactivator species TIF-2/GRIP-1/NCoA-2 and SRC-1/NCoA-1 presently under examination.

Applicants appreciate the Examiner's indication that the rejection of claims 1 to 26 under 35 U.S.C. § 102(b) and 103(a) as allegedly anticipated by, or obvious in view of, the cited reference by DiRenzo et al. has been withdrawn.

Regarding the amendment

The title of the abstract has been amended at page 76 to replace "ABSTRACT OF THE INVENTION" with "ABSTRACT OF THE DISCLOSURE." This amendment to the abstract does not add new matter. The Examiner is therefore respectfully requested to enter the amendment.

Regarding the Election of Species Requirement

Applicants respectfully remind the Examiner that, in the event that a linking claim such as generic claim 1 is found allowable, subject matter directed to non-elected species previously withdrawn from consideration must be rejoined and examined for patentability (MPEP 809).

Regarding the objection to the abstract

The abstract of the disclosure is objected to for being entitled "ABSTRACT OF THE INVENTION." The title of the abstract is herein amended to "ABSTRACT OF THE DISCLOSURE" to conform with 37 C.F.R. § 1.72. In view of this amendment, Applicants respectfully request that this objection be withdrawn.

Regarding the Rejection under 35 U.S.C. § 112, second paragraph

The rejection of claims 1 to 26 under 35 U.S.C. § 112, second paragraph, as allegedly vague and indefinite due to the phrase "nuclear hormone receptor activities" in claims 1, 2, 11 and 18 is respectfully traversed.

The Office Action alleges that the recited "nuclear hormone receptor activities" are vague and indefinite. According to the Office Action, the specification indicates that the term includes an indirect signaling pathway "not directly associated with nuclear hormone receptor function." The Office Action concludes that the metes and bounds of the recited nuclear hormone receptor "activities" would be unclear to the skilled person.

Applicants maintain that the meaning of the term "nuclear hormone receptor activities" is clear to the skilled person in view of the specification. In particular, nuclear hormone receptor activities are those activities resulting from activation of a pathway by a nuclear hormone receptor; therefore, in contrast to the assertion in the Office Action, these activities are all "associated with" nuclear hormone receptor function. See, for example, the specification at page 13, lines 24-31, which discloses an indirect signaling pathway "activated by the nuclear hormone receptor." Furthermore, in view of the specification, one skilled in the art understands that the recited nuclear hormone receptor activities include activities resulting from activation of transcription through cognate hormone response elements as well as activities which result without activation of cognate nuclear hormone response elements. In this regard, the specification teaches, for example, that nuclear hormone receptor activity can occur in the absence of cognate hormone response element activation, for example, through an AP-1 or STAT-mediated pathway (page 13, line 22, to page 14, line 8) or a pathway mediated by another hormone receptor. Thus, in view of the specification, it is understood that the term "nuclear hormone receptor activities" refers to biological effects mediated through a nuclear hormone receptor. It is further understood that this term includes effects occurring through activation of nuclear hormone response elements as well as other biological effects resulting upon ligand binding or other regulation of a nuclear hormone receptor.

In sum, the phrase "nuclear hormone receptor activities" is clear and unambiguous to the skilled person in view of the specification. Accordingly, Applicants respectfully request that the Examiner reconsider and remove the rejection of claims 1 to 26 under 35 U.S.C. § 112, second paragraph.

Regarding the rejection under 35 U.S.C. § 102(b)

The rejection of claims 1 to 3, 6 to 8, 11 to 13, 16 and 19 under 35 U.S.C. § 102(b) as allegedly anticipated by Chen and Evans is respectfully traversed.

The Office Action indicates that Chen and Evans report identification of SMRT as a corepressor for retinoid and thyroid hormone receptors. Chen and Evans indicate that the association of SMRT corepressor with receptors is destabilized by ligand (Chen and Evans; page 454, column 2, third paragraph). The Office Action further indicates that Chen and Evans report the interaction of SMRT with receptor-DNA complexes in the presence of the PAF coactivator (page 457, column 2, second paragraph). The Office Action concludes that the claimed methods are anticipated in view of the description of addition of ligand to a test complex which includes the nuclear hormone receptor TR, the coactivator PAF and the corepressor SMRT in the presence of a nuclear hormone response element (oligoprobe).

Applicants respectfully traverse the above rejection, submitting that the claimed methods are novel over Chen and Evans. Applicants would emphasize that the claims are directed to methods of identifying an effective agent by assaying for coactivator association with a test complex in addition to assaying for corepressor association with a test complex, where an effective agent is identified by the combination of coactivator association and corepressor association with the test complex. In short, an effective agent is identified according to a method of the invention by the combination of coactivator association and corepressor association with the same test complex. See, for example, specification at page 9, lines 2-6, which discloses that certain ligands or other compounds can induce the simultaneous association of a coactivator and corepressor with a nuclear hormone receptor, and page 11, lines 3-7, which indicates that dissociated ligands can be identified based on their ability of induce coactivator recruitment and simultaneous corepressor retention.

The cited art does not teach each and every element of the claimed invention. In particular, Chen and Evans do not teach an effective agent which results in coactivator association and corepressor association with a nuclear hormone receptor, as required for identifying an effective agent that dissociates nuclear hormone receptor activities according to a method of the invention. Rather, Chen and Evans emphasize repeatedly that the corepressor

SMRT dissociates from nuclear hormone receptor upon ligand binding. As indicated in the abstract, ligand causes destabilization (i.e. dissociation) of SMRT with receptors. Furthermore, Chen and Evans report that binding of ligand to retinoic acid receptor (RAR) or thyroid receptor (TR) reduces receptor interaction with SMRT (page 454, second column, first complete sentence); and that the association of full-length RAR or its ligand-binding domain with SMRT is blocked by ligand (page 454; second column, second full paragraph; and Figure 2a). Similarly, when analyzing the interaction of SMRT and receptor-DNA complexes, Chen and Evans conclude that addition of ligand releases SMRT from RXR/RAR-response element complex and that addition of thyroid hormone ligand disrupts the interaction of SMRT with RXR/TR on a thyroid receptor DNA element (page 456, second column, first complete paragraph). From these data, Chen and Evans conclude that "SMRT may be recruited to target promoters by interaction with DNA-binding unliganded receptors in a ligand-reversible matter (page 456, second column, first complete paragraph, concluding sentence; emphasis added). Chen and Evans also state at page 457, final paragraph, that "We have shown that ligand causes the dissociation of SMRT from the receptor, triggering the activation process. This could be followed (or be coincident) with an induced conformational change in the C-terminal transactivation domain (τc, also called AF-2), allowing association with co-activators." From the above, it is clear that Chen and Evans do not teach coactivator association and corepressor association with the same test complex or the claimed methods of identifying an effective agent that dissociates nuclear hormone receptor activities, which require coactivator association combined with corepressor association following treatment of receptor with an agent.

In sum, Chen and Evans report dissociation of SMRT upon ligand binding to RAR and TR receptors but do not teach an effective agent that results in corepressor association with a nuclear hormone receptor test complex. Chen and Evans further do not teach a method of identifying an effective agent based on coactivator association and corepressor association to a test complex following treatment of nuclear hormone receptor with an agent. Failing to teach all the elements of the invention, the cited reference by Chen and Evans cannot anticipate the claimed methods.

In view of the above remarks, Applicants respectfully request that the Examiner reconsider and remove the rejection of claims 1 to 3, 6 to 8, 11 to 13, 16 and 19 under 35 U.S.C. § 102(b) as allegedly anticipated by Chen and Evans.

Regarding the rejection of claims 1 to 26 under 35 U.S.C. § 103

The rejection of claims 1 to 3, 6 to 8, 11 to 13, 16 and 19 under 35 U.S.C. § 103(a) as allegedly obvious over Chen and Evans (1995) in view of Chen et al. (1996) is respectfully traversed.

As indicated above, Chen and Evans report that the association of SMRT with receptors is destabilized by ligand. The Office Action acknowledges that Chen and Evans do not teach assaying the SRC-1 coactivator but cites Chen et al. (1996) as reporting that silencing is relieved by dissociation of corepressor and transcription activated by recruitment of a transcriptional activator such as SRC-1.

Applicants submit that the cited references, neither alone nor in combination, teach or suggest the claimed methods of identifying an effective agent that dissociates nuclear hormone receptor activities by assaying for coactivator association together with corepressor association, where coactivator association combined with corepressor association indicates an effective agent that dissociates nuclear hormone receptor activities. Chen and Evans, which has been discussed above, at best reports dissociation of SMRT from receptor complexes following addition of ligand but does not teach or suggest SMRT or other corepressor association combined with coactivator association, as required to identify an effective agent according to a method of the invention. Neither does Chen et al. (1996) cure what is lacking in the primary reference. Rather, as acknowledged in the Office Action, Chen et al. (1996) report that "the effect of hormone in nuclear receptor signaling is to relieve silencing by inducing a dissociation of corepressor(s) and to activate transcription by recruiting transcriptional coactivator(s)" (page 7570, last complete paragraph; emphasis added). Thus, in contrast to the claimed methods, Chen et al. (1996) report that a given hormone results in dissociation of corepressor follwed by coactivator association. Similarly, Chen et al. (1996) at best report that SMRT interacts with unliganded receptor heterodimers (page 7567, abstract). However, the cited reference does not teach or suggest that an effective agent can be identified by coactivator association together with corepressor

Absent such a teaching or suggestion, the cited references, neither alone nor in combination, teach or suggest the claimed methods.

Accordingly, the Examiner is respectfully requested to remove the rejection of claims 1 to 3, 6 to 8, 11 to 13, 16 and 19 under 35 U.S.C. § 103 as allegedly obvious over Chen and Evans (1995) in view of Chen et al. (1996).

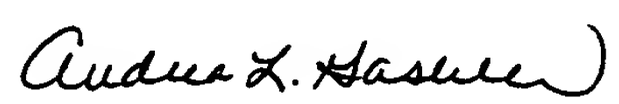
CONCLUSION

Applicants submit that the claims are in condition for allowance and respectfully request a notice to that effect. Should the Examiner have any questions in connection with this application, he is invited to call the undersigned agent or Cathryn Campbell.

To the extent necessary, a petition for an extension of time under 37 C.F.R. 1.136 is hereby made. Please charge any shortage in fees due in connection with the filing of this paper, including extension of time fees, to Deposit Account 502624 and please credit any excess fees to such deposit account.

Respectfully submitted,

MCDERMOTT WILL & EMERY LLP



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